

REMARKS/ARGUMENTS

Claims 1, 3, 16, and 19 have been amended; claims 12-14 have been cancelled. Thus, claims 3-11, 15, 17, 18, 27-28, and 46 are pending. Applicant has amended claim 1 to include the limitations from original claim 12. Claims 3, 16, and 19 have been amended to correct certain typographic informalities per the Examiner's suggestion. For example, the capitalization from amino acid names has been removed and the designation "OBzl benzyl" has been changed to "OBzl". Accordingly, Applicant submits that no new matter has been added. Entry of the amendment is respectfully requested.

Claims 1-19, 27, 28, and 46 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over *Lipton* (United States Patent 5,028,592) in view of *Kauvar* (United States Patent 5,786,336). The Examiner has determined that it "would have been obvious...to synthesize the KPV tripeptide in it's diamide form in the diacetyl KPV tripeptide synthesize methods of *Lipton* because *Kauvar* teach[es] [that] it was known that the diamide form of tripeptide synthesis allows for such tripeptides to optimally exert intracellular effectis..." *Office Action*, page 6. Applicant respectfully traverse the rejection.

*Lipton* is directed to a lysine-proline-valine ("KPV") tripeptide for the treatment of inflammation. *Lipton* provides a single synthetic method of preparing a KPV tripeptide, which involves preparing protected intermediates and purification of the tripeptide on a silica gel column. *Lipton*, col.7, 11.45-67 to col.8, 11.1-62. As conceded by the Examiner, *Lipton* does not teach KPV tripeptide diamides or any methods of synthesizing tripeptide amides. *Office Action*, pages 6-7. Nor does *Lipton* offer any new, improved methods of synthesizing tripeptides with increased yields.

*Kauvar* is directed to a method of improving the effect of a chemotherapeutic by administering glutathione analogs. *Kauvar*, col.1, ll. 15-22. *Kauvar* also teaches enhanced intracellular effects through glutathione diesters or diamides. *Kauvar*, col.2, ll.37-40. As conceded by the Examiner, *Kauvar* does not disclose KPV tripeptides or KPV tripeptide diamines or their method of synthesis. *Office Action*, pages 6-7.

First, one skilled in the art would not have looked to the collective teachings of the cited art for methods of making KPV tripeptide diamides as in the claimed invention. The Examiner is of the opinion that *Lipton* is not limited to the preparation of KPV tripeptides. To support his contention, the Examiner cites several passages from *Lipton* indicating that biological activity may be present even if the peptide structure is changed. For example, "[i]t is believed that many changes may be made in the amino acid sequence of the peptides and still obtain a protein which exhibits a biologically functional equivalent pharmacologic activity." *Office Action*, page 4, emphasis added.

Contrary to the Examiner's contention, the claimed invention is not directed to changing the amino acid sequence to arrive at different tripeptides. Instead, the KPV tripeptides of the claimed invention are derivatized to include two amide groups. There is no change whatsoever to the amino acid sequence or peptide backbone in the claimed invention. Thus, one skilled in the art would not have looked to *Lipton* for a method of preparing amide-derivatized KPV tripeptides.

Nor would one skilled in the art look to *Kauvar*, alone or in combination with *Lipton*, to arrive at the claimed method. *Kauvar* is directed to the biological properties of glutathione,

a tripeptide having the sequence Glu-Cys-Gly. While *Kauvar* discloses that tripeptides such as glutathione may contain amide functionality, there is no disclosure whatsoever of methods of synthesizing or modifying any tripeptide, let alone selectively adding amide groups to specific amino acid residues. Accordingly, the collective art of record does not teach tripeptide diamide synthesis, and certainly not KPV tripeptide diamide synthesis.

Second, there is nothing in the collective teachings of the cited art which suggest that the claimed method would have resulted in a higher yield of KPV tripeptide. The Examiner believes that Applicant "provide[d] no indication of what protective groups/reagents in the claimed invention have been modified versus that of *Lipton* in order to arrive at the asserted unexpected result" of increased yield. *Office Action*, page 5. Quite to the contrary, Applicant has shown "that [with] an appropriate selection of the protective groups, the reagents to be used and the reaction sequence makes it possible to increase the yield from 33% [(the yield cited in *Lipton*)] to more than 70%." Application, ¶¶ [0052] and [0053].

In part, it is the use of different protective groups for each lysine amine in the claimed invention that aids in this increase in yield. In contrast, *Lipton* teaches a lysine residue wherein both amine groups are protected with the same benzyloxycarbonyl protecting groups (see *Lipton*, example 1). There is no disclosure in *Lipton* that different protecting groups could be used. This is important because each of the protecting groups can independently be removed at different points in the KPV tripeptide diamide synthesis. Amended claim 1 clearly illustrates these independent deprotections and subsequent chemical modifications which contribute to the

increased overall yield.

Nor is there any disclosure in *Kauvar* that different protecting groups could be used. *Kauvar* merely describes traditional peptide synthesis using F-moc protected starting materials. There is no teaching that different protective groups could be introduced. Moreover, the yields recited in *Kauvar*, which range from 6% to 44%, show little, if any, improvement in general tripeptide synthesis over *Lipton*. *Kauvar*, Table I.

Claim 46 distinguishes the claimed invention even further in that it expressly disclaims any final purification step. *Lipton*, on the other hand, requires chromatographic purification on a silica gel column. *Lipton*, col.8, ll.36-40.

Accordingly, one skilled in the art would have not found it obvious to use different protecting groups during tripeptide synthesis or eliminate the use of chromatographic purification to increase overall reaction yield, especially when the prior art teaches using the same protecting groups and chromatographic purification.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that he/she telephone Applicant's attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

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Respectfully submitted,

By 

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